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Maternal antenatal methylxanthine (including caffeine) treatment for improving preterm outcomes (Protocol)

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[Intervention Protocol]

Maternal antenatal methylxanthine (including caffeine) treatment for improving preterm outcomes

Charles Christoph C Roehr[1], Rupjani Banerjee[1], Ana Alarcon-Allen[1], Eugene Dempsey[2]

[1]Newborn Services, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. [2]Neonatology, Cork University Maternity Hospital, Wilton, Ireland

Contact address: Charles Christoph C Roehr, Newborn Services, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. charles.roehr@paediatrics.ox.ac.uk, ccroehr@icloud.com.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To review and summarise the existing evidence of the relationship between maternal methylxanthine (including caffeine) consumption (or by any other method of administration) versus no intervention, placebo or a different methylxanthine, before birth with the intention to influence outcomes in preterm newborns, with particular focus on cardiorespiratory adaptation at birth and long-term neurodevelopmental outcomes.

BACKGROUND

Description of the condition

The transition from fetal to newborn life involves major physiological adaptations essential for survival. In the fetus, the lungs are fluid-filled and gas exchange occurs across the placenta. The pulmonary vascular resistance is high and pulmonary blood flow is low. After birth, the infant is separated from the placental circulation when the umbilical cord is clamped. This leads to a switch to pulmonary gas exchange and a major cardiovascular reorganisation within minutes after birth (Hooper 2015). Many preterm infants will need assistance with breathing after birth, as they suffer from an excess of lung fluid which needs to be cleared, and reduced surfactant pools, limiting lung compliance (Hillman 2012). It is therefore crucial to support the infant in the perinatal period to optimise successful lung aeration and an uneventful cardiorespiratory transition after birth. At present, efforts to support the preterm infant have focused largely on postnatal management. Recent data from studies suggest that ante- and perinatal treatments may further help to improve postnatal management (Dekker 2017). One of these treatments is maternal antenatal methylxanthine (including caffeine), when applied transdermally, orally or by intravenous route. The treatment with methylxanthines is proposed to improve respiratory drive (frequency of breaths), respiratory mechanics (depth of breaths) and to help overcome apnoea (i.e. reduce the length of breath-holding episodes).

Description of the intervention

The Royal College of Obstetricians and Gynaecologists (RCOG) states that the "current advice issued by the National Institute for Health and Care Excellence (NICE) is that pregnant women should limit their consumption of caffeine to 300 milligrams a day" (NICE 2008; RCOG 2011). A large prospective observational study by the Care Study Group in 2010 concluded that antenatal caffeine consumption was associated with fetal growth restriction, particularly with daily caffeine intake of 200 mg or more (CARE Study Group 2010). Our National Health Service (NHS) website advise pregnant women to restrict their daily caffeine intake to 200 mg (NHS 2018). Taking these guidelines into account, we propose to look into the studies where pregnant women received methylxanthine (including caffeine) by oral, intravenous or other routes (e.g. dermal patch) in the last month prior to preterm delivery, in doses less than or equal to 200 mg with the intention to positively influence the outcome of the preterm baby.

How the intervention might work

Methylxanthines, in particular caffeine and theophylline, have been used in the treatment of apnoea of prematurity. They act by stimulating the respiratory centre in the medulla, increasing sensitivity to carbon dioxide, increasing skeletal muscle tone, increasing diaphragmatic contractility, increasing minute volume, increasing metabolic rate and increasing oxygen consumption (Abdel-Hady 2015). Caffeine is also a central nervous system stimulant and a somnolytic agent. Caffeine, through its adenosine blocking effect, modulates several neurotransmitters like dopamine, serotonin, noradrenaline, acetylcholine and gamma-aminobutyric acid (Abdel-Hady 2015; Shrestha 2017). Caffeine also stimulates the myocardium and increases heart rate, thus improving cardiac output, stroke volume and mean arterial blood pressure (Shrestha 2017).

At the molecular level, methylxanthines are adenosine receptor antagonists as well as being phosphodiesterase inhibitors (Shrestha 2017). Adenosine is a purine nucleoside in the brain and has four receptors - A1, A2a, A2b and A3 (Shrestha 2017). These receptors, through their effects on adenylate cyclase can cause central respiratory depression, sedation and smooth muscle constriction (Shrestha 2017). Caffeine (a trimethylxanthine), is a specific inhibitor of at least A1 and A2a and thus manifests its effects in preterm neonates (Shrestha 2017). Caffeine's effect as a phosphodiesterase inhibitor and a calcium channel binder is at a much higher level and further research is needed on these pathways of action (Shrestha 2017). A systematic review showed that caffeine's therapeutic window is wider and that it has fewer adverse effects compared to theophylline, making it the more preferred first-line therapy for apnoea of prematurity (Schoen 2014).

There is evidence that maternally consumed caffeine passes the placental barrier freely (Sengpiel 2013). Animal studies have shown that administration of methylxanthine (aminophylline) to pregnant rabbits may enhance fetal lung maturation by stimulating pulmonary surfactant production prior to delivery (Ayromlooi 1981). There is evidence from neonatal randomised controlled trials (RCTs) that early methylxanthine (including caffeine) administration (within 72 hours of birth) is safe and results in reduced apnoea and improved respiratory outcomes (Schmidt 2006). A recent pilot RCT of very early caffeine administered before two hours of age compared to after 12 hours of life showed an improvement in haemodynamics in preterms in terms of blood pressure, systemic blood flow and right ventricular output (Katheria 2015). In models of perinatal brain injury, caffeine is neuroprotective against periventricular white matter injury and hypoxic ischaemic encephalopathy (Kreutzer 2014). Methylxanthines have also been shown to improve rate of mortality and neurodevelopmental outcomes in preterms (Khurana 2017). However, still very little is known regarding maternal methylxanthine intake in the last month prior to delivery and its effects on the cardiorespiratory adaptation of the preterm infant and long-term neurological outcomes.

Why it is important to do this review

About 15 million premature babies (defined as born less than 37 weeks of gestation) are born worldwide each year. These infants represent 11% of all newborn babies (Howson 2013). Despite three decades of multiple advances in the field of neonatal medicine, preterm birth is still the second largest cause of death in children under five years of age (Lawn 2004). One of the goals of 'Healthy People 2020' is to reduce low birthweight (LBW) and very low birthweight (VLBW) (HHS 2010).

European consensus guidelines on the management of respiratory distress syndrome (RDS) reiterates the importance of antenatal corticosteroids in the role of RDS prevention. Antenatal corticosteroids also improve the cardiac function following preterm delivery (Hillman 2012). However, the transition from fetus to newborn is one of the most complex physiological adaptations involving multiple organs. Initiation of breathing and maintenance of adequate respiratory efforts is one of the major contributors to a successful adaptation. The preterm newborn is significantly disadvantaged compared to the term newborn during this adaptation phase due to the lack of adequately developed lungs, leading to difficulty with ventilation, reduced surfactant and reduced compliance (Hillman 2012). However, the adaptation of preterm lungs has been helped postnatally by positive pressure ventilation and methylxanthine. Multiple studies, including RCTs (Schmidt 2006), have proven the benefit of methylxanthines on preterm infant health, as illustrated above. Given the complex nature of the transition and adaptation of the fetus to the preterm newborn and the numerous factors that play a role in this, earlier support in this transition process may positively affect cardiorespiratory adaptation. A smooth transition will aid improved cardiorespiratory and neurodevelopmental outcomes, improving mortality and morbidity - a 'Healthy People 2020' goal (HHS 2010). One such mode of

support might be the antenatal administration of methylxanthine (including caffeine) to support the transition from fetus to preterm newborn. The authors noted a significant gap in the literature, in terms of systematic reviews on this topic, and therefore propose to review the body of evidence available currently, with the aim of improving knowledge of whether a preterm infant benefits from maternal-to-fetal transfer of methylxanthines, prior to birth.

OBJECTIVES

To review and summarise the existing evidence of the relationship between maternal methylxanthine (including caffeine) consumption (or by any other method of administration) versus no intervention, placebo or a different methylxanthine, before birth with the intention to influence outcomes in preterm newborns, with particular focus on cardiorespiratory adaptation at birth and long-term neurodevelopmental outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We plan to include all published, unpublished and ongoing randomised controlled trials (RCTs) that compare the administration of maternal caffeine versus no intervention, placebo or a different methylxanthine in the last month of pregnancy, including up to the point of delivery, in women who give birth to preterm infants. We will also include studies comparing the administration of a methylxanthine (other than caffeine) to placebo or no intervention. We will also include quasi-randomised and cluster-randomised trials, but we are aware of the increased risk of bias in these type of trials (please refer to the sections on Unit of analysis issues and Sensitivity analysis). We will also make sure we report if there were trials controlled for dietary intake of caffeine.

Types of participants

1. Pregnant women in the last month of their pregnancy who are at risk of giving birth to a preterm infant and received methylxanthines (including caffeine) or placebo prior to giving birth (by any mode of delivery) before or at 36 + 6 weeks of gestation.

2. Preterm infants (including 23 to 36 + 6 weeks gestational age) born to the above mentioned cohorts of women involved in the studies.

Please note that though the preterm infant is being included for outcome measures, they are not receiving any intervention. The intervention is being given to the mother prior to the infant being born.

We will exclude the following conditions from our review.

1. Cases of antepartum haemorrhage, cord prolapse or other causes of perinatal asphyxia leading to hypoxic ischaemic encephalopathy.
2. Any chromosomal anomalies.
3. Any congenital heart disease.
4. Any surgical conditions, such as congenital diaphragmatic hernia.
5. Apgar score less than 5 at five minutes of age.

Types of interventions

Administration of methylxanthines (including caffeine) or a placebo or no intervention in the last month of pregnancy in women who had a preterm delivery. The methylxanthines (including caffeine) could have been administered either by oral intake, intravenous infusion or any other route (e.g. dermal patch) in doses less than or equal to 200 mg of caffeine (one mug of instant coffee is 100 mg).

Types of outcome measures

Primary outcomes

The effect of maternal methylxanthine (including caffeine) intake in the last month on the preterm infant's cardiorespiratory transition. In particular, we will focus on:

1. the need for and duration of intubation and ventilation;
2. the incidence of arterial hypotension (mean arterial blood pressure less than the gestational age or need for fluid resuscitation or inotropic support);
3. neurodevelopmental outcome at two years of age, assessed by the Bayley Scales of Infant and Toddler Development (BSITD; Bayley 2006), or other standardised neurodevelopmental assessment tools.

Secondary outcomes

The effect of maternal methylxanthine (including caffeine) intake in the last month (including the perinatal period) on:

1. incidence of stillbirths;
2. the need for any pulmonary surfactant;
3. the incidence and severity of apnoea within the first 120 hours of life;
4. bronchopulmonary dysplasia, defined by the need for supplemental oxygen at a postmenstrual age of 36 weeks;

5. haemodynamically significant patent ductus arteriosus (based on echocardiographic evidence) needing pharmacologic closure or surgical ligation;
6. ultrasonographic signs of brain injury, including intraventricular haemorrhage (grades 3 and 4 of which will be categorised as severe), cystic periventricular leukomalacia, haemorrhagic parenchymal infarction, moderate to severe posthaemorrhagic ventricular dilatation or echodensity persisting > three to four weeks;
7. necrotising enterocolitis;
8. retinopathy of prematurity;
9. neonatal death;
10. total duration of stay in the neonatal intensive care unit (NICU);
11. any adverse maternal outcomes, e.g. insomnia, headache, nausea, diarrhoea, etc.

Search methods for identification of studies

The following methods section of this protocol is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We will search Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist.
The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link.
Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:
1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that will be fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).
In addition, we will search ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform for unpublished, planned and ongoing trial reports, using the search terms listed in Appendix 1.

Searching other resources

We will search the reference lists of retrieved studies. We will not apply any language or date restrictions.

Data collection and analysis

The following methods section of this protocol is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

A minimum of two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a further review author.
We will create a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We will design a form to extract data. For eligible studies, at least two independent review authors will extract the data using the agreed form. The information that we will extract from the trial reports will also include trial dates, sources of trial funding, trialist declarations of interest, etc. We will also report if there are trials controlled for dietary intake of caffeine. We will resolve discrepancies through discussion or, if required, we will consult a further review author. We will enter data into Review Manager software (Review Manager 2014), and check for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

A minimum of two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a further assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.
We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.
We will assess the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane*

Handbook for Systematic Reviews of Interventions (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

We will assess the quality of the evidence using the GRADE approach, as outlined in the GRADE handbook, in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons. We will compare the intervention to either placebo, another intervention or to no intervention. We will assess the effect of maternal methylxanthine (including caffeine) intake in the last month of pregnancy on the preterm infant's cardiorespiratory transition. In particular, we will focus on:

1. the need for and duration of intubation and ventilation;
2. the incidence of arterial hypotension (mean arterial blood pressure less than the gestational age or need for fluid resuscitation or inotropic support;
3. neurodevelopmental outcome at two years of age, assessed by the Bayley Scales of Infant and Toddler Development (BSITD; Bayley 2006), or other standardised neurodevelopmental assessment tools.

We will use the GRADEpro Guideline Development Tool to import data from Review Manager 5 in order to create 'Summary of findings' tables (Review Manager 2014). We will produce a summary of the intervention effect and a measure of quality for each of the above outcomes using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio (RR) with 95% confidence intervals (CIs).

Continuous data

For continuous data, we will use the mean difference (MD) if outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

If we include cluster-randomised trials in the analyses along with individually randomised trials, we will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 16.3.4 or 16.3.6; Higgins 2011), using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Other unit of analysis issues

Other unit of analysis issues: should our search reveal trials in Pregnancy and Childbirth which include outcomes for multiple gestations (twin pregnancies), we will report the special methods to analyse data relating to multiple gestations as outlined in Cochrane Pregnancy and Childbirth methodological guidelines and the*Cochrane Handbook for Systematic Reviews of Interventions* (Sections 9.3.7 and 16.3; Higgins 2011).

If we identify studies that include more than two intervention groups, we will use 'multiple-treatments meta-analysis' methods (Section 16.6.3; Higgins 2011).

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial

will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau², I² and Chi² statistics. We will regard heterogeneity as substantial if I² is greater than 30% and either Tau² is greater than zero, or there is a low P value (less than 0.10) in the Chi² test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using Review Manager 5 software (Review Manager 2014). We will use a fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect, i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use a random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with 95% CIs, and the estimates of Tau² and I².

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use a random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Extreme preterm deliveries (23 + 0 to 26 + 6 weeks) versus early preterm deliveries (27 + 0 to 31 + 6).
2. Early preterm deliveries (27 + 0 to 31 + 6 weeks) versus late preterm deliveries (32 + 0 to 36 + 6 weeks).
3. Intake of maternal methylxanthine (including caffeine) for less than or equal to 24 hours before preterm delivery versus intake of maternal methylxanthine (including caffeine) for more than 24 hours before preterm delivery.
4. The dose of intake of maternal methylxanthine (including caffeine) being less than or equal to 100 mg versus the dose of intake of maternal methylxanthine (including caffeine) being more than 100 mg to a maximum of 200 mg.

We will use the following outcomes in all of the above subgroup analyses.

The effect of maternal methylxanthine (including caffeine) intake in the last month of pregnancy on the preterm infant's cardiorespiratory transition. In particular, we will focus on:

1. the need for and duration of intubation and ventilation;
2. the incidence of arterial hypotension (mean arterial blood pressure less than the gestational age or need for fluid resuscitation or inotropic support);
3. neurodevelopmental outcome at two years of age, assessed by the Bayley Scales of Infant and Toddler Development (BSITD; Bayley 2006), or other standardised neurodevelopmental assessment tools.

We will assess subgroup differences by interaction tests available within Review Manager 5 (Review Manager 2014). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I² value.

If we identify studies that include more than two intervention groups, we will use 'multiple-treatments meta-analysis' methods (Section 16.6.3; Higgins 2011).

Sensitivity analysis

We will carry out a sensitivity analysis with aims to explore the effects of the trial quality assessed by allocation concealment and other risk of bias components, by omitting studies rated as 'high risk of bias' for these components. We will restrict this to the primary outcomes.

If we identify quasi-randomised trials we will do a sensitivity analysis to see if this makes any difference to the overall analysis.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search terms for ClinicalTrials.gov and ICTRP

caffeine AND pregnancy
caffeine AND antenatal
caffeine AND prenatal
methylxanthine(s) AND pregnancy
methylxanthine(s) AND antenatal
methylxanthine(s) AND prenatal

CONTRIBUTIONS OF AUTHORS

- Guarantor of the review: Dr Charles Christoph Roehr
- Conceiving, designing and co-ordinating the review: Dr Charles Roehr
- First draft of the protocol: Dr Rupjani Banerjee
- Subsequent review and editing of the first draft of the protocol: Drs Rupjani Banerjee, Charles Roehr, Ana Alarcon Allen and Eugene Dempsey
- Edited final draft of the protocol: Drs Rupjani Banerjee, Charles Roehr, Ana Alarcon Allen and Eugene Dempsey

DECLARATIONS OF INTEREST

- Dr Charles Christoph Roehr: none known
- Dr Rupjani Banerjee: none known
- Dr Ana Alarcon Allen: none known
- Dr Eugene Dempsey is Chief Investigator for a European funded trial (Seventh Framework Program, European Commission) on management of hypotension in preterm infants.